UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,135	10/18/2006	Amar Lulla	PAC/23225 US (4137-00600)	8688

30652 7590 09/24/2008

CONLEY ROSE, P.C.
5601 GRANITE PARKWAY, SUITE 750
PLANO, TX 75024

EXAMINER	
WESTERBERG, NISSA M	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
09/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,135	LULLA ET AL.	
	Examiner	Art Unit	
	Nissa M. Westerberg	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/25/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 - 35* is/are pending in the application.

4a) Of the above claim(s) *4 - 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 - 3, 11 - 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/11/06, 7/25/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of alendronic acid in the reply filed on July 25, 2008 is acknowledged. Applicant traverse the species election requirement on the basis that the Examiner's alleged species do not represent species but in fact represent individual compounds within a species because each of the alleged species can contain contain only one member. Also, the examiner has failed to establish lack of unity and the combination as recited in independent claim 1 serves as both the common and special technical feature that is generic to the alleged species. The rationale presented in paragraph 3 of the Restriction Requirement is insufficient and it appears that the Examiner is impermissibly applying U.S. restriction practice to this national stage PCT application.

These arguments are not persuasive. In the instant application, "bisphosphonic acid derivatives" is the genus, which is composed of various species, which in the instant case are different, single chemical compounds. The genus of "bisphosphonic acid derivatives" is broad and includes derivatives, prodrugs, solvates and/or hydrates of the compounds, and the first two in particular could significantly alter the structure of the compound being recited.

The requirement is still deemed proper and is therefore made FINAL.

Comments and Notes

2. Claim 25 adds additional limitations to the "binder" of claim 1. Claim 1 recites the required presence of "an aqueous binder". While there are no other binders are recited in claim 1 to cause confusion regarding which ingredient is being specified in claim 25, it is kindly suggested that claim 25 be amended to recite "the aqueous binder".

Claim Objections

3. Claims 22 and 23 are objected to because of the following informalities: it appears that a typographical error is present in the name of the compound "sodium starch glycollate." Appropriate correction is required.

Claim Rejections - 35 USC § 112 – 1st Paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1 – 3 and 11 – 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. None of the derivatives, prodrugs, solvates or hydrates other than the compounds specifically named, either in the specification or claims, meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus of derivatives or prodrugs of bisphosphonic acid encompassed by the claim, since there is no description of the structural relationship of these derivatives provided in the specification and Applicant has not provided a description as to how the base molecule may be changed while remaining a derivative or prodrug. The stoichiometry of the solvate or hydrate and nature of the solvate used have not been described to such a extent to support the full genus of hydrates or solvates beyond the specific hydrates explicitly named, such as alendronate sodium trihydrate.

Claim Rejections - 35 USC § 112 2nd Paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 34 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "substantially free of degradation products" is a

relative phrase which renders the claim indefinite. The term "substantially free" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. What level of degradation products would render the composition no longer substantially free of degradation products and/or over what time period the compositions contained an acceptable level of degradation products is not defined in the claim or in the specification.

8. Claim 35 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "intimately mixing" is a relative term which renders the claim indefinite. The term "intimately" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. What level of mixing and/or level of association between the bisphosphonic acid derivative and at least one carbohydrate alcohol is required to achieve an "intimate mix" of these components is not defined in the claim or the specification.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1 – 3, 11 – 22, 25 – 32 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Jasprova (WO 02/03963).

Jasprova discloses a tablet obtained by direct compression of alendronic acid or its pharmaceutically acceptable salts, a diluent, a dry binder, a disintegrating agent and a lubricant wherein the diluent is a combination of at two diluents except lactose (p 8, ¶ 3). Lactose is known to interact with sodium alendronate, especially in the presence of water, to hasten its degradation (p 2, ¶ 3). The at least two diluents except for lactose comprise 20 – 80% by weight of the tablet of microcrystalline or pulverized cellulose or calcium hydrogenphosphate and 0.001 to 50% by weight of mannitol (a carbohydrate alcohol), modified starches and phosphates or hydrogenphosphate or alkali or alkaline earth metals (p 8, ¶4). A preferred composition is 10 – 50% by weight mannitol and 30 – 70% by weight microcrystalline cellulose (MCC; p 9, ¶3). However, a modified starch together with mannitol also results in a product with appropriate quality (p 10, ¶ 3). In formulations 3A – 3D (p 13, ¶ 6 - p 14), compositions including about 8.5% starch by weight are prepared, about 10% by weight bisphosphonic acid compound, varying amounts of mannitol (65%, 30%, 20% and 10%) and granulated MCC (15%, 50%, 60% and 70%) and 1% by weight of the lubricant/glidant magnesium stearate is used.

Shown on p 17 are data regarding the stability over time for the various formulations indicating that at 3 and 6 months, the amount of active ingredient in the

tablets was the same as when first prepared, indicating a lack of formation of degradation products as required in claim 34.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1 – 3 and 11 – 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jasprova (WO 02/03963) in view of Flash-Ner-Barak et al. (WO 02/00204).

Jasprova discloses a tablet obtained by direct compression of alendronic acid or its pharmaceutically acceptable salts, a diluent, a dry binder, a disintegrating agent and a lubricant wherein the diluent is a combination of at two diluents except lactose (p 8, ¶ 3). Lactose is known to interact with sodium alendronate, especially in the presence of water, to hasten its degradation (p 2, ¶ 3). The at least two diluents except for lactose comprise 20 – 80% by weight of the tablet of microcrystalline or pulverized cellulose or calcium hydrogenphosphate and 0.001 to 50% by weight of mannitol (a carbohydrate alcohol), modified starches and phosphates or hydrogenphosphate or alkali or alkaline earth metals (p 8, ¶4). A preferred composition is 10 – 50% by weight mannitol and 30 – 70% by weight microcrystalline cellulose (MCC; p 9, ¶3). However, a modified starch together with mannitol also results in a product with appropriate quality (p 10, ¶ 3). In formulations 3A – 3D (p 13, ¶ 6 - p 14), compositions including about 8.5% starch by weight are prepared, about 10% by weight bisphosphonic acid compound, varying amounts of mannitol (65%, 30%, 20% and 10%) and granulated MCC (15%, 50%, 60% and 70%) and 1% by weight of the lubricant/glidant magnesium stearate is used.

Shown on p 17 are data regarding the stability over time for the various formulations indicating that at 3 and 6 months, the amount of active ingredient in the tablets was the same as when first prepared, indicating a lack of formation of degradation products as required in claim 34.

Jasprova does not disclose a capsule formulation or the use of sodium starch glycolate as the disintegrant.

Flash-Ner-Barak et al. discloses that when formulating a tablet or capsule, the other excipients present in rapidly expanding pharmaceutical composition are determined, in part, by whether a tablet or capsule is being formulated (p 9, ¶3). Flash-Ner-Barak et al. also discloses that the inventive composition includes a superdisintegrant, disintegrants which swell upon contact with water, such as sodium starch glycolate (p 6, ¶ 3). The swelling of the dosage form provides a dosage form that remains in the stomach for an extended period of time and over time, particles of the dosage form degrade or erode away and enter the small intestine (p 8, ¶ 2), providing a delayed release of the active ingredient to the upper GI tract where alendronate is best absorbed (p 4, ¶ 4). The amount of superdisintegrant can vary from about 10% to about 75% by weight (p 7, ¶ 3).

It would have been obvious to one of ordinary skill in the art to prepare a dosage form as taught by Jasprova using alendronic acid, no lactose, MCC and mannitol which exhibits excellent stability of the active ingredient over time, and to use the superdisintegrant sodium starch glycolate in a tablet or capsule dosage form, taught by Flash-Ner-Barak et al. to allow for a dosage form which swells in the stomach and

allows for the delayed release of the active ingredient to the upper GI tract for better absorption of the active ingredient over time.

15. Claims 1 – 3 and 11 – 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jasprova and Flash-Ner-Barak et al. as applied to claims 1 – 3 and 11 – 34 above, and further in view of Katdare et al. (WO 95/29679).

Jasprova and Flash-Ner-Barak et al. disclose tablet or capsule composition of bisphosphonic acid derivatives such as alendronic acid that can comprise MCC, mannitol, a superdisintegrant such as sodium starch glycolate and magnesium stearate. In both references, the dry ingredients are mixed together in a dry state.

Neither reference discloses the mixing of the active ingredient with the carbohydrate alcohol, followed by a wet granulation process.

Katdare et al. discloses a process comprising forming a powder blend of the bisphosphonic acid active ingredient with diluents, wet granulating the powder blend with water to form granules, which are then dried and the compressed into the desired tablet form with a lubricant (p 2, ln 10 – 24). The carbohydrate alcohol mannitol is disclosed as a preferred diluent (p 5, ln 32 – 33).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to use the wet granulation procedure of Katdare et al. to prepare the pharmaceutical dosage form as taught by Jasprova and Flash-Ner-Barak et al. as all of the formulations prepare dosage forms of overlapping constituents.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nissa M. Westerberg whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8 a.m. - 4 p.m. ET. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

NMW